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10/520,962	11/28/2005	Naomi Burke Anker	MS0012YP	4932

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EXAMINER
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OLSON, ERIC

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1623

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12/21/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/520,962	Applicant(s) ANKER ET AL.	
	Examiner Eric S. Olson	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 07 November 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 1-3 and 5-24 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 25 is/are allowed.
- 6) ☒ Claim(s) 4 and 26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **Detailed Action**

This office action is a response to applicant's communication submitted November 7, 2007 wherein an election is made in response to the previous requirement for restriction. This application is a national stage application of PCT/US03/21493, filed July 8, 2003, which claims benefit of provisional application 60/394734, filed July 11, 2002.

Claims 1-26 are pending in this application.

### **Restriction**

The previous requirement for restriction incorrectly identified claims 1-4 as belonging to group I, drawn to a compound of formula I. In fact, these claims are seen to be drawn to a therapeutic method that is generic to groups II-VII. Therefore group I is seen to consist of claims 25 and 26. If any of claims 1-4 are found to be allowable, any claims of groups II-VII that depend from or otherwise incorporate all the limitations of the allowed claims will be rejoined. In a telephone conversation with Sylvia Ayler on December 12, 2007, Applicant confirmed that an election of group I, claims 25 and 26 is still desired in view of this correction.

Applicant's provisional election with traverse of group I, drawn to a pyrazolopyridazine, filed November 7, 2007, is acknowledged. Applicant's arguments of record with respect to the aforementioned traversal are acknowledged and found to be not persuasive to remove the requirement for restriction. Applicant argues that there is

no burden for searching all claims together and that the claims should be rejoined as there is an allowable generic claim in the application. This reasoning does not apply to claims 1-3 which do not incorporate all the limitations of allowed claim 25, or to claims 5-24, which depend from claim 1.

Claims 1-3 and 5-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on November 7, 2007.

Claims 4, 25, and 27 as amended are examined on the merits herein.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim recites the phrase, " $\text{—C}_0\text{—C}_{60}\text{alkyl}$ ". An alkyl group is a hydrocarbon and must contain at least one carbon atom. Therefore it is not clear to one skilled in the art what a  $\text{C}_0$  alkyl is. This defect renders claim 26 indefinite. Note that claims 1-3 and their dependent claims, if rejoined, would be indefinite for the same reason.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: who the compound of formula (I) is administered to.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 26 is rejected under 35 U.S.C. 102(b) as being anticipated by Uchida et al. (Reference included with PTO-892) Uchida et al. discloses the synthesis of pyrrolo-pyridazines by condensation of a pyrrole-diketone (all compounds **6** and **7**) with hydrazine. (p. 241, right column, last paragraph, p. 244, left column, first paragraph) Products synthesized in this manner include compounds 10(a-c) which fall within the limits of instant claim 26. (p. 244, left column, top of column, compound **10**) Furthermore, the compounds **6** and **7** as shown on p. 241, right column, top of column, include additional embodiments of **10** wherein  $R^1 = \text{Ph}$  and/or  $R^2 = \text{p-OCH}_3$ , which also fall within the claimed invention. Therefore the claimed invention is anticipated by Uchida et al.

### **Withdrawn Claims 5-24**

Claims 5-24 are withdrawn and do not incorporate all of the limitations of instant claim 4 or 25. However, if said claims were to be amended in such as way as to allow for rejoinder, they would be subject to the following grounds of rejection under 35 USC 112:

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating certain disorders, does not reasonably provide enablement for prevention or prophylaxis of said disorders, for example neuropathic and nociceptive pain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the

claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. "Prevention" as discussed herein is interpreted to mean the complete blocking of all symptoms or effects of a disorder for an indefinite period of time.

Nature of the invention: The claimed invention is drawn to a therapeutic method for treatment or prevention of a disorder. Merriam-Webster's Collegiate Dictionary (reference included with PTO-892) defines "prevent" as meaning, "to deprive of power or hope of acting or succeeding," or "to keep from happening or existing." This definition is taken as representing the ordinary usage of the term "preventative". In order to deprive something of power or hope of acting or succeeding, the preventative agent must be completely effective. "Prevention" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disorder for an indefinite period of time. Merely slowing the onset of disease or making the disease less likely would still leave it with "power or hope of acting or succeeding," and thus not qualify as prevention.

The state of the prior art: Certain alpha-2-delta agonists are known in the art to be useful for treating neuropathic and nociceptive pain. They are not known to be useful as preventative agents in the sense being used herein. In general, prevention of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective.

Furthermore the analgesic effects of alpha-2-delta ligands are temporary, and no permanent effects on the subject's nervous system have been reported. Drugs which

exhibit a permanent curative analgesic effect (i.e. permanently relieving a painful syndrome) are not known, except in cases where the relief of pain is a secondary effect to the permanent cure of the underlying disease (e.g. pain caused by cancer or microbial infection). Similarly, there is no precedent in the prior art for any alpha-2-delta ligand, PDEV inhibitor, combination thereof, or compound possessing similar biological activity, which is capable of permanently preventing the occurrence of pain after the drug is cleared from the patient's system. Similarly, no drug could permanently prevent the occurrence of all pathological conditions having neuropathic pain as a symptom, as many of these conditions (e.g. postsurgical pain, phantom limb syndrome) arise from physical trauma to the nervous system and no drug is capable of preventing physical trauma.

In fact, no mechanism is known by which drugs of the kind described in the claimed invention could exert any analgesic effects after being cleared from a subject's system, as they must generally be present within the subject's body in order to be effective. Furthermore, it is generally desired within the art that an analgesic treatment not exert permanent effects on a patient's nervous system, as such permanent effects may very well be deleterious.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of

treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

- 1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?
- 2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms? For example, will a metastatic cancer eventually adapt to overcome treatments directed to preventing it from metastasizing into the bone? Or will a case of osteoporosis or rheumatoid arthritis ultimately progress to a point where symptoms develop regardless of which therapy is administered.
- 3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antibiotics, chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

Furthermore, there are many different syndromes which may lead to pain as one symptom. According to the Merck Manual of Diagnosis and Therapy, 17<sup>th</sup> edition (Reference included with PTO-892) neuropathic pain may be caused by multiple underlying causes, generally classified as either deafferentiation pain or sympathetically maintained pain. (p. 1371, right column, third paragraph) Specific syndromes causing neuropathic pain include, but are not limited to postherpetic neuralgia, phantom limb pain, root avulsions, painful traumatic neuropathy, painful polyneuropathy, central pain syndromes, postsurgical pain syndromes, and postthoractomy syndrome. (p. 1372, left column, 4<sup>th</sup> paragraph) Furthermore, it is stated that, "Treatment applied without concern for diagnosis, rehabilitation, and psychosocial issues has a limited chance of success." (p. 1372, left column, 3<sup>rd</sup> paragraph) Nociceptive pain, arising from tissue damage or inflammation, additionally has many different causes. Thus a treatment that is prophylactic or curative for one particular pain syndrome is unlikely to thus be curative for every pain syndrome, as a cure or prevention would involve the permanent reversal or prevention of the underlying syndrome rather than the temporary relief of painful symptoms.

The Breadth of the claims: In the absence of an explicit definition in Applicant's specification, the claims are given their broadest reasonable interpretation, as discussed above. Merely slowing the onset of disease or making the disease less likely would still leave it with "power or hope of acting or succeeding," and thus not qualify as prevention.

The amount of direction or guidance presented: No guidance is given in the specification suggesting any reason to believe that the claimed compounds are uniquely useful as preventative agents.

The presence or absence of working examples: No working examples are given of any therapeutic methods whatsoever.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

The quantity of experimentation necessary: As mentioned above, the short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness for prevention of disease. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy. In particular, one skilled in the art, in order to practice the invention for prevention of disease, would need to know whether the preventative effect remains potent over the long term.

Based on the state of the prior art, one skilled in the art would believe that the only way to permanently cure a case of neuropathic pain is to remove the underlying cause. Similarly, the only way to permanently prevent neuropathic pain is to permanently prevent every disorder having neuropathic pain as a symptom. A cure is possible in certain instances, such as surgical decompression of carpal tunnel syndrome. Other forms of neuropathic pain, such as that arising from phantom limb

syndrome, cannot be permanently cured or prevented and must be treated through palliative means. The applicant's disclosure does nothing to challenge this conclusion. Although the applicant discloses a pharmaceutical composition which is potentially useful for the palliative treatment of neuropathic pain, nothing in the disclosure suggests that there exists any method by which the claimed composition would be useful for the curative or prophylactic treatment of neuropathic pain.

In order to practice the claimed invention for the curative or prophylactic treatment of pain, one skilled in the art would need to independently develop curative and preventative therapies for a variety of disorders, including but not limited to those recited previously. It is unlikely that every such syndrome would be adequately cured or prevented by a pharmaceutical treatment. Rather, certain treatments would involve surgery and/or physical therapy as an essential component for the cure or prevention of neuropathic pain. Developing such therapeutic methods in the absence of any guidance from applicant's disclosure constitutes undue experimentation. Thus the applicant's disclosure is not enabling for the curative or prophylactic treatment of pain, particularly neuropathic pain.

In order to answer these questions in the absence of any existing data, one skilled in the art, in order to practice the invention, would undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or monkeys, or a human clinical trial. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional

burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Administering the claimed compounds for a period of years to a suitable subject population is an undue amount of experimentation needed in order to practice the full range of the claimed invention. As prevention in the full sense is an extremely high bar for any clinical outcome, there is no reason to believe that the therapy would be successful, and any actual success would be a surprising and unpredictable result.

*Genentech*, 108 F.3d at 1366, states that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the nature of the invention, Applicants fail to provide information sufficient to practice the claimed invention for the prevention of various disorders.

### **Conclusion**

Claims 4 and 26 are rejected. Claim 25 is seen to be allowable.

Reasons for the indication of allowable subject matter are as follows:

The subject matter of claim 25 is seen to be adequately enabled and supported under 35 USC 112 by the specification as originally filed. For example, the examples

on pp. 30-88 disclose the claimed compounds and how to make them. One of ordinary skill in the art would also know that these compounds are useful drugs for the treatment of nociceptive and neuropathic pain, and for epilepsy, based on the alpha-2-delta ligand activity disclosed on pp 89-148 of the specification, and by analogy with known alpha-2-delta ligands such as gabapentin.

Furthermore the claimed compounds are not seen to be taught or fairly suggested by the prior art. Although pyrrolo-pyridazines have been synthesized in the prior art, for example those of Uchida et al., none of the compounds of claim 25 are taught in the prior art. Furthermore, there would be no motivation for one skilled in the art to modify them to arrive at the claimed invention as they are not disclosed to have any biological activity or therapeutic utility.

Therefore claim 25 is seen to be allowable over the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Eric Olson



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